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(21) International Application Number: PCT/US00/11748 (22) International Filing Date: 1 May 2000 (01.05.00) (30) Priority Data: 60/183,057 4 May 1999 (04.05.99) US 09/552,631 19 April 2000 (19.04.00) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/552,631 (CON) Filed on 19 April 2000 (19.04.00) (71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GRUBB, Gary, S. [US/US]; 825 Briarwood Road, Newtown Square, PA 19073 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San Diego, CA 92129 (US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US).		(74) Agents: KODROFF, Cathy, A. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
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<p>(I)</p>			
(57) Abstract This invention relates to cyclic combination therapies and regimens utilizing substituted indoline derivative compounds that are antagonists of the progesterone receptor having general structure (I) wherein: R ₁ , and R ₂ are chosen independently from each other from H, OH; OAc; alkylaryl; alkylheteroaryl; 1-propynyl; 3-propynyl; and optionally substituted alkyl, O(alkyl); aryl; or heteroaryl groups; or R ₁ and R ₂ are joined to form a ring comprising -CH ₂ (CH ₂) _n CH ₂ - where n = 0-5; -CH ₂ CH ₂ CMe ₂ CH ₂ CH ₂ -; -O(CH ₂) _m CH ₂ - where m = 1-4; O(CH ₂) _p O- where p = 1-4; -CH ₂ CH ₂ OCH ₂ CH ₂ -; -CH ₂ CH ₂ N(H or alkyl)CH ₂ CH ₂ -; or R ₁ and R ₂ together comprise a double bond to CMe ₂ ; C(cycloalkyl), O, or C(cycloether); R ₃ is H, OH, NH ₂ , COR ^A ; or optionally substituted alkenyl or alkynyl groups; R ^A = H or optionally substituted alkyl, alkoxy, or aminoalkyl groups; R ₄ = H, halo, CN, NH ₂ , or optionally substituted alkyl, alkoxy, or aminoalkyl; R ₅ is selected from optionally substituted benzene ring; a five or six membered heterocyclic ring; a 4 or 7-substituted indole or a substituted benzothiophene; or pharmaceutically acceptable salt thereof. These methods of treatment may be used for contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, or minimization of side effects or cyclic menstrual bleeding. Additional uses of the invention include stimulation of food intake.			

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CONTRACEPTIVE COMPOSITIONS CONTAINING 3,3-SUBSTITUTED INDOLINE DERIVATIVES
AND USES THEREOF**Field of the Invention**

5 This invention relates to regimens of administering compounds, which are antagonists of the progesterone receptor in combination with a progestin, an estrogen, or both.

Background of the Invention

10 Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

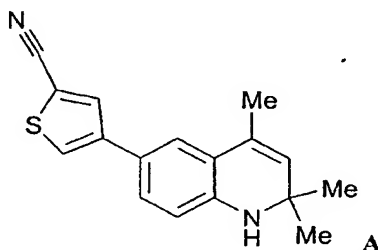
15 The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene
20 promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

 A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist.

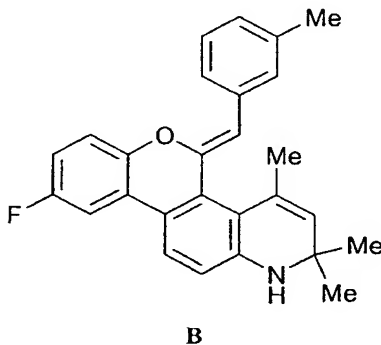
25 PR antagonists may be used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N.Y. Acad. Sci.*, **261**, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997, published July 4, 1996). PR antagonists may also be useful for the treatment of
30 hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub:

Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis (Kettel, et al, *Fertility and Sterility*, **56**, 402, 1991). PR antagonists
5 may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (U.S. Patent No. 5,719,136). PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna, et al, *Ann. N.Y. Acad.*
10 *Sci.*, **761**, 224, 1995).

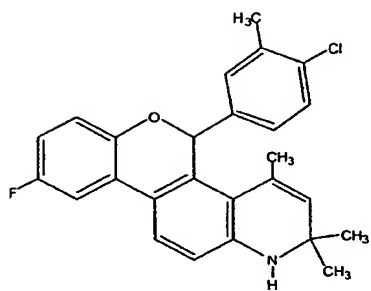
Jones, *et al*, (U.S. Patent No. 5,688,810) describe the PR antagonist dihydroquinoline A.



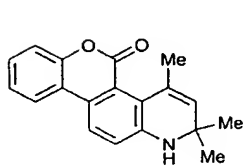
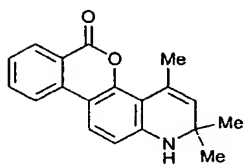
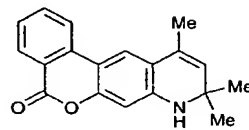
15 Jones, *et al*, described the enol ether B (U.S. Patent No. 5,693,646) as a PR ligand.



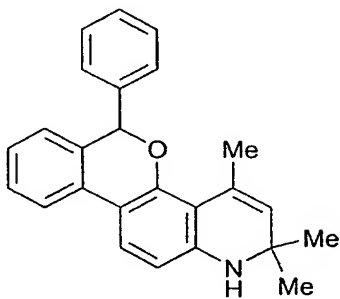
Jones, *et al*, described compound **C** (U.S. Patent No. 5,696,127) as a PR ligand.

**C**

Zhi, *et al*, described lactones **D**, **E** and **F** as PR antagonists (*J. Med. Chem.*, 41, 291, 1998).

**D****E****F**

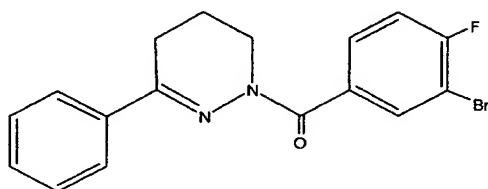
Zhi, *et al*, described the ether **G** as a PR antagonist (*J. Med. Chem.*, 41, 291, 1998).



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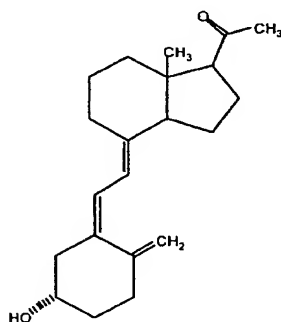
G

Combs, *et al.*, disclosed the amide **H** as a ligand for the PR (*J. Med. Chem.*, **38**, 4880, 1995).



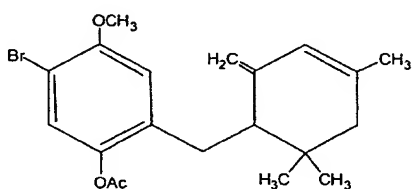
H

Perlman, *et al.*, described the vitamin D analog **I** as a PR ligand (*Tet. Letters*, **35**, 2295, 1994).



I

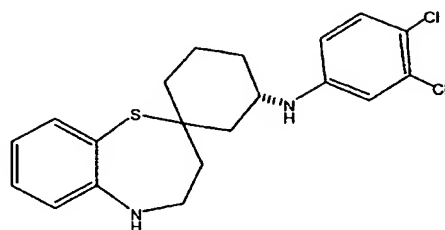
Hamann, *et al.*, described the PR antagonist **J** (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995).



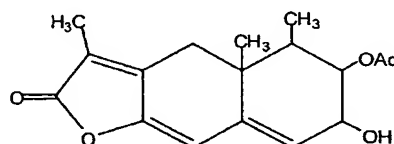
J

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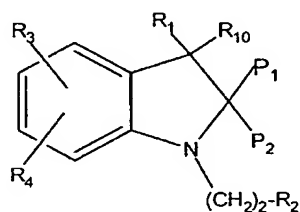
Chen, *et al.*, described the PR antagonist **K** (Chen, *et al.*, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).

**K**

Kurihari, *et al.*, described the PR ligand **L** (*J. Antibiotics*, **50**, 360, 1997).

**L**

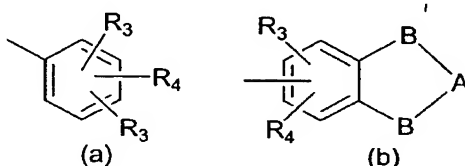
Elliott (Smith Kline Beecham) claimed the generic indoline **M** as potential endothelin receptor antagonists (WO 94/14434). The patent does not claim indolines and lacks the appropriate 5-aryl substitution, i.e. CN and NO₂.

**M**

R₁, R₁₀, P₁ and P₂ = H, 1-8 C alkyl, Ph
 n = 0
 R₃ = H
 R₂ = H
 R₄ = Ar (substituted)

wherein: R₄ = H, Ar, R₁₁, OH, 1-5 C alkoxy (opt. substd. by OH, OMe or halogen),

- S(O)_qR₁₁, N(R₆)₂, XR₁₁, halogen or NHCOR₆; X = (CH₂)_n, O, NR₆ or S(O)_q; n = 0-6; q = 0-2; R₆ = H or 1-4 C alkyl; R₁₁ = 1-8 C alkyl, 2-8 C alkenyl or 2-8 C alkynyl (all optionally substituted); Ar = (i) optionally substituted phenyl or benzo-fused group of (a) or (b); or (ii) naphthyl, indoyl, pyridyl, thienyl, oxazolindyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, pyrrolyl or pyrimidyl, all optionally substituted by one or more R₁ or R₂ groups.



10

A = CO or (C(R₆)₂)_m B = CH₂ or O

- U.S. Patent No. 5,521,166 (Grubb) teaches cyclophasic hormonal regimens comprising an antiprogestin and a progestin wherein the progestin is administered in the alternating presence and absence of an antiprogestin. The disclosed regimens also provide for use of an estrogen for a period of from 2 to 4 days to prevent breakthrough bleeding.

Description of the Invention

- This invention provides combination therapies and dosing regimens utilizing antiprogesterational agents in combination with one or more progestational agents. This invention further provides methods of treatment and dosing regimens further utilizing in combination with these antiprogesterins and progestins, an estrogen, such as ethinyl estradiol.

- These regimens and combinations may be administered to a mammal to induce contraception or for the treatment and/or prevention of secondary amenorrhea, dysfunctional bleeding, uterine leiomyomata, endometriosis; polycystic ovary syndrome, carcinomas and adenocarcinomas of the endometrium, ovary, breast,

colon, and prostate. Additional uses of the invention include stimulation of food intake. The uses herein for the treatment and/or prevention of the conditions or diseases described above includes the continuous administration or periodic discontinuation of administration of the invention to allow for minimization of effective dose or minimization of side effects or cyclic menstrual bleeding.

The use of this invention for contraception includes administration, preferably orally, to a female of child bearing age an antiprogestin in combination with an estrogen or progestin or both. These administration regimens are preferably carried out over 28 consecutive days, with a terminal portion of the cycle containing administration of no progestins, estrogens or anti-progestins.

The progestins of these combinations may be administered alone or in combination with an estrogen for the first 14 to 24 days of the cycle, the progestins being administered at a dosage range equal in progestational activity to about 35 μg to about 150 μg levonorgestrel per day, preferably equal in activity to from about 35 μg to about 100 μg levonorgestrel per day. An antiprogestin may then be administered alone or in combination with an estrogen for a period of 1 to 11 days to begin on any cycle day between day 14 and 24. The anti-progestin in these combinations may be administered at a dose of from about 2 μg to about 50 μg per day and the estrogen may be administered at a dose of from about 10 μg to about 35 μg per day. In an oral administration, a package or kit containing 28 tablets will include a placebo tablet on those days when the antiprogestin or progestin or estrogen is not administered.

In a preferred embodiment of this invention, the progestins of this invention may be administered alone or in combination with an estrogen for the initial 18 to 21 days of a 28-day cycle, followed by administration of an antiprogestin, alone or in combination with an estrogen, for from 1 to 7 days.

The estrogen to be used in the combinations and formulations of this invention is preferably ethinyl estradiol.

Progestational agents useful with this invention include, but are not limited to, levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone,

dienogest, drospirenone, nomegestrol, or (17-deacetyl)norgestimate. Among the preferred progestins for use in the combinations of this invention are levonorgestrel, gestodene and trimegestone.

5 Examples of orally administered regimens of this invention over a 28 day cycle include administration of a progestational agent solely for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 100 μ g of levonorgestrel. An antiprogestin compound of this invention may then be administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28. It is most preferred that the daily dosages of each relevant active ingredient be incorporated into a combined, single daily dosage unit, totaling 28 daily units per 28-day cycle.

In another regimen, a progestational agent may be coadministered for the first 21 days at a daily dose equal in progestational activity to from about 35 to about 150 μ g levonorgestrel, preferably equal in activity to from about 35 to about 100 μ g levonorgestrel, with an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 μ g. This may be followed as described above with an antiprogestin administered at a daily dose of from about 2 to 50 mg from day 22 to day 24, followed by no administration or administration of a placebo for days 25 to 28.

25 Still another regimen within the scope of this invention will include coadministration from days 1 to 21 of a progestational agent, the progestational agent, preferably levonorgestrel, being administered at a daily dose equal in progestational activity to from about 35 to about 100 μ g levonorgestrel, and an estrogen, such as ethinyl estradiol, at a daily dose range of from about 10 to about 35 μ g. This will be followed on days 22 to 24 by coadministration of an antiprogestin (2 to 50 mg/day) and an estrogen, such as ethinyl estradiol, at a daily dose of from about 10 to about 35 μ g. From day 25 to day 28, this regimen may be followed by no administration or administration of a placebo.

This invention also provides kits or packages of pharmaceutical formulations designed for use in the regimens described herein. These kits are preferably designed for daily oral administration over a 28-day cycle, preferably for one oral administration per day, and organized so as to indicate a single oral formulation or
5 combination of oral formulations to be taken on each day of the 28-day cycle. Preferably each kit will include oral tablets to be taken on each the days specified, preferably one oral tablet will contain each of the combined daily dosages indicated.

According to the regimens described above, one 28-day kit may comprise:

- a) an initial phase of from 14 to 21 daily dosage units of a
10 progestational agent equal in progestational activity to from about 35 to about 150 μg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 μg levonorgestrel;
- b) a second phase of from 1 to 11 daily dosage units of an antiprogesterin compound of this invention, each daily dosage unit containing an
15 antiprogesterin compound at a daily dosage of from about 2 to 50 mg; and
- c) optionally, a third phase of an orally and pharmaceutically acceptable placebo for the remaining days of the cycle in which no antiprogesterin, progesterin or estrogen is administered.

A preferred embodiment of this kit may comprise:

- a) an initial phase of 21 daily dosage units of a progestational agent
20 equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably equal in progestational activity to about 35 to about 100 μg levonorgestrel;
- b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogesterin compound of this invention, each daily dosage unit containing an
25 antiprogesterin compound at a daily dosage of from about 2 to 50 mg; and
- c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Another 28-day cycle packaging regimen or kit of this invention comprises:

- a) a first phase of from 18 to 21 daily dosage units of a progestational
30 agent equal in progestational activity to about 35 to about 150 μg levonorgestrel,

preferably equal in activity to from about 35 to about 100 μ g levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 μ g; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of this invention at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the kit described above may comprise:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μ g levonorgestrel, preferably equal in activity to from about 35 to about 100 μ g levonorgestrel, and, as an estrogen, ethinyl estradiol at a daily dose range of from about 10 to about 35 μ g; and

b) a second phase of 3 daily dosage units for days 22 to 24 of an antiprogestin administered at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dose units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

A further 28-day packaged regimen or kit of this invention comprises:

a) a first phase of from 18 to 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μ g levonorgestrel, preferably equal in activity to from about 35 to about 100 μ g levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μ g;

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μ g; and

c) optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0-9 days in the 28-day cycle in which no progestational agent, estrogen or antiprogestin is administered.

A preferred embodiment of the package or kit just described comprises:

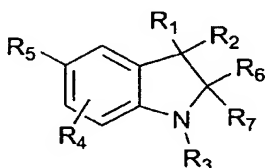
- a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel, preferably from about 35 to about 100 μg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg ;
- b) a second phase of 3 daily dose units for days 22 to 24, each dose unit containing an antiprogesterin of this invention at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg ; and
- c) optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

In each of the regimens and kits just described, it is preferred that the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is administered. It is also understood that the daily dose units described are to be administered in the order described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle. It is further preferred that each package or kit comprise a pharmaceutically acceptable package having indicators for each day of the 28-day cycle, such as a labeled blister package or dial dispenser packages known in the art.

In this disclosure, the terms anti-progestational agents, anti-progestins and progesterone receptor antagonists are understood to be synonymous. Similarly, progestins, progestational agents and progesterone receptor agonists are understood to refer to compounds of the same activity.

These dosage regimens may be adjusted to provide the optimal therapeutic response. For example, several divided doses of each component may be administered daily or the dose may be proportionally increased or reduced as indicated by the exigencies of the therapeutic situation. In the descriptions herein, reference to a daily dosage unit may also include divided units which are administered over the course of each day of the cycle contemplated.

Compounds of this invention that may be used as the anti-progestational agents in the kits, methods and regimens herein are those of the Formula I:



I

5

wherein:

R_1 and R_2 are chosen independently from H, alkyl, substituted alkyl; OH; O(alkyl); O(substituted alkyl); OAc; aryl; optionally substituted aryl; heteroaryl; optionally substituted heteroaryl; alkylaryl; alkylheteroaryl; 1-propynyl; or 3-propynyl;

10

or R_1 and R_2 are joined to form a ring comprising one of the following:

$-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$; $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$; $-\text{O}(\text{CH}_2)_m\text{CH}_2-$; $\text{O}(\text{CH}_2)_p\text{O}-$; $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$; $-\text{CH}_2\text{CH}_2\text{N}(\text{H or alkyl})\text{CH}_2\text{CH}_2-$;

n is an integer from 0 to 5;

15

m is an integer from 1 to 4;

p is an integer from 1 to 4;

or R_1 and R_2 together comprise a double bond to $=\text{C}(\text{CH}_3)_2$; $=\text{C}(\text{C}_3\text{-C}_6\text{ cycloalkyl})$, $=\text{O}$, or $=\text{C}(\text{cycloether})$, wherein cycloether is selected from tetrahydrofuranyl or hexahydropyranyl;

20

R_3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, alkynyl or substituted alkynyl, or COR^A ;

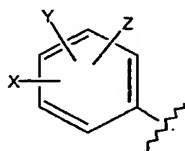
R^A is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

25

R_4 is H, halogen, CN, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R_5 is selected from the groups a), b) or c):

a) R_3 is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



X is selected from halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, S(O)alkyl, S(O)₂alkyl, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO₂, C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^B, OCOR^B, or NR^CCOR^B;

R^B is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl:

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkyl;

or
b) R_3 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR₆ and containing one or two independent substituents from the group including H, halogen, CN, NO₂ and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, COR^D, or NR^ECOR^D;

R^D is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

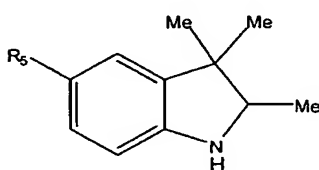
R₆ is H or C_1 to C_3 alkyl;

or
c) R⁵ is an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, the moiety being optionally substituted by from 1 to 3 substituents selected from halogen,

lower alkyl, CN, NO₂, lower alkoxy, or CF₃; wherein R₆ and R₇ are independently chosen from H, methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, cyclohexyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

or pharmaceutically acceptable salt thereof.

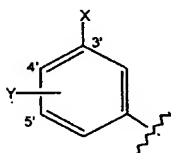
- 5 A preferred set of antiprogestin compounds of this invention is depicted by structure II:



II

- 10 wherein:

R₅ is a disubstituted benzene ring containing the substituents X, and Y as shown below:

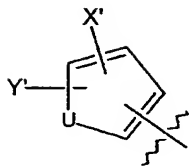


- 15 X is selected from halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5-membered heterocyclic ring containing 1 to 3 heteroatoms, or C₁ to C₃ thioalkoxy;

Y is a substituent on the 4' or 5' position selected from H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkyl;

or

- 20 R₅ is a five membered ring having the structure:



U is O, S, or NR₆,

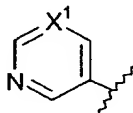
R₆ is H, or C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from halogen, CN, NO₂, C₁ to C₃ alkyl or C₁ to C₃ alkoxy;

5 Y' is selected from the group H, F, CN, NO₂ or C₁ to C₄ alkyl;

or

R₅ is a six-membered ring with the structure:



X' is N or CX²;

10 X² is halogen, CN or NO₂;

or pharmaceutically acceptable salt thereof.

The antiprogesterin compounds of the formulations and regimens of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I and II the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

20 The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with 1 or 2 carbon-carbon double bonds and containing 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms; "alkynyl" group is intended to cover both

straight- and branched-chain alkyl group with at least 1 or 2 carbon-carbon triple bonds and containing 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO₂, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include but not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, and phenanthryl.

The term "substituted aryl" refers to an aryl as just defined having 1 to 4 substituents from the group including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidiny, piperaziny, 2-oxopiperidiny, azepiny, pyrrolidiny, imidazolyl, pyridyl, pyraziny, pyrimidiny, pyridaziny, oxazolyl, isoxazolyl, morpholiny, indolyl, quinoliny, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholiny, thiamorpholiny sulfoxide, and isoquinoliny.

The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having 1 to 4 substituents selected from the group which includes halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "thioalkyl" is used herein to refer to the SR group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms. The term "alkoxy" refers to the OR group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms. The term "aryloxy" refers to the OR group, where R is aryl or substituted aryl, as defined above. The term "alkylcarbonyl" refers to the RCO group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. The term "alkylcarboxy" indicates the COOR group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups, containing 1 to 8 carbon atoms, which may be either the same or different and the point of attachment is on the nitrogen atom. The term "halogen" refers to Cl, Br, F, or I.

The antiprogestational compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*.

When the active compounds of these regimens are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent,

syrops containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The pharmacologically active agents of this invention may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

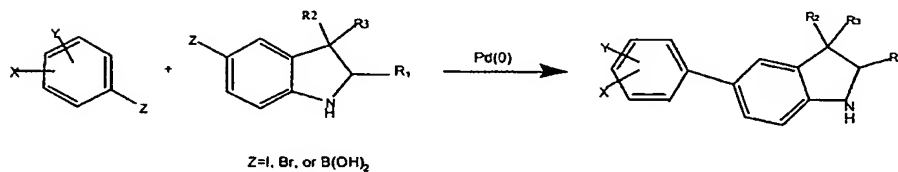
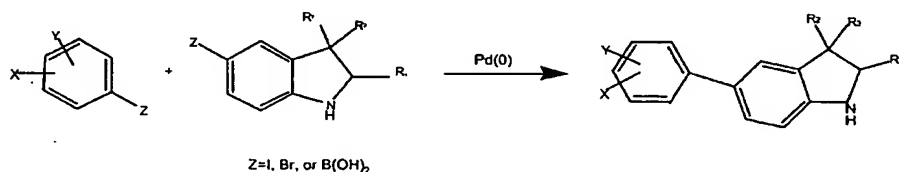
The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringeability exists. It must be stable under

conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

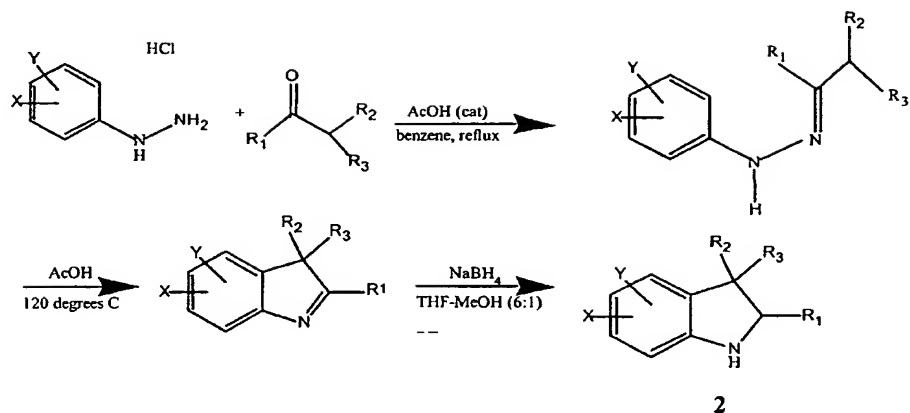
The compounds of this invention can be prepared by the procedures outlined in the Schemes illustrated below:

Typically the antiprogestin compounds of this invention are prepared in a convergent manner as shown in **Scheme 1**, by a suitable coupling reaction. For example, a palladium mediated coupling of an aryl halide with an aryl boronic acid provides the desired bi-aryl substituted target. The choice of the aryl halide-aryl boronic acid combination is established experimentally.

Scheme 1



As outlined in **Scheme 2**, the “right side” of the antiprogestin compounds of this invention may be prepared by following the procedure described of Letcher, R. M. et. al., *J. Chem. Soc. Perkin Trans.*, 1993, Vol. 1, pp. 939 - 944.

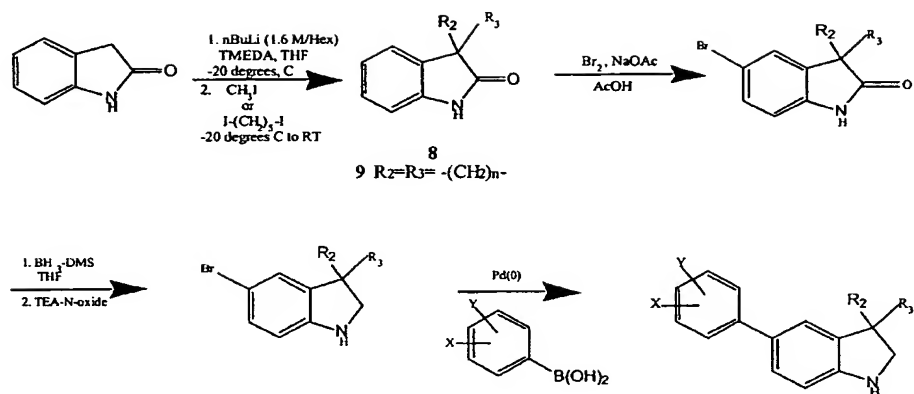
Scheme 2

As an example the right side template, 2, is prepared by condensing an appropriately substituted phenyl hydrazine and a suitable ketone to give the corresponding hydrazone. This material is cyclized to an imine in refluxing acetic acid and then reduced to the desired indoline template 2. Examples 1-7 and 10-20 were prepared by this route using the appropriate ketone.

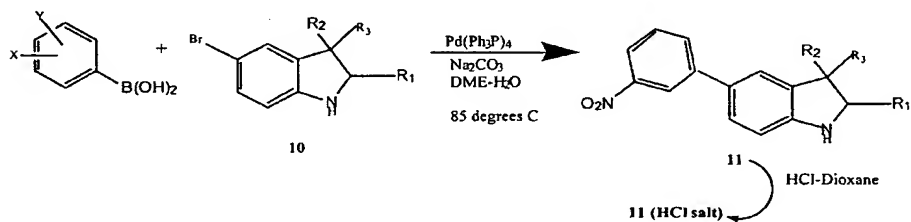
Alternatively the right side template may be prepared as outlined in Scheme 3.

10 The commercially available oxindole is di-alkylated at C-3 by using an appropriate base and the corresponding alkyl halide to give the 3,3-dialky-oxindole, 8, or the spiro-cyclic oxindole 9. These oxindoles are then brominated under standard conditions and the carbonyl group is reduced to the desired methylene using a hydride mediated reduction. The timing of the aryl coupling and the reduction of the 2-

15 position carbonyl are established experimentally.

Scheme 3

The right side templates are coupled with an appropriate aryl boronic acid using an appropriate palladium (0) catalyst, **Scheme 4**. For example compound **10** is coupled under standard Suzuki conditions with an appropriately substituted aryl-boronic acid to afford compound **11**.

Scheme 4

10

The compounds of this invention, are stable semi-solids and are conveniently converted into their corresponding salts by treatment with acid. Example 1, compound **11** ($\text{R}_1=\text{R}_2=\text{R}_3=\text{Me}$), when treated with HCl in dioxane affords the HCl salt (Example 2) as a white solid. The racemic indolines can be separated into their enantiomers by Chiral HPLC, to provide the individual enantiomers in > 98% EE.

15

This invention may be further understood by the following non-limiting examples.

5

EXAMPLE 1**2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole****5-Bromo-2,3,3-trimethyl-2,3-dihydro-1H-indole**

This compound was prepared by the procedure of Letcher, R. M. et. al., *J. Chem. Soc. Perkin Trans.*, 1: 939 – 944, 1993.

10 To a solution of 4-bromo-phenyl hydrazine hydrochloride (2.59g, 11.6 mmol) and 3-methyl-2-butanone (1.0 g, 11.6 mmol) in 20 mL benzene was added acetic acid (catalytic amount) and the resulting solution was refluxed with azeotropic removal of H₂O for 14 h. The reaction mixture was cooled to room temperature and concentrated. The resulting semi-solid was extracted in acetic acid and refluxed for
15 12 hours. The reaction mixture was cooled to room temperature and concentrated. The semi-solid residue was extracted in ether and neutralized with K₂CO₃. The ether layer was dried and concentrated. The resulting solid imine was dissolved in THF-MeOH (6:1), cooled to 0°C and sodium borohydride (0.5 g, 13.2 mmol) was added. The solution was allowed to warm to room temperature and stirred for 0.5 hours. The
20 reaction mixture was poured into 15% aqueous HCl and then made basic with K₂CO₃. The organic layer was separated, washed with brine, dried (Na₂SO₄), and concentrated. The crude product was purified by column chromatography (SiO₂, hexane-ethyl acetate 9:1). The product was isolated as an orange liquid (2.1 g, 75%):
25 ¹H-NMR (CDCl₃) δ 1.03 (s, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 3H), 3.50 (q, *J* = 6.6 Hz, 1H), 3.70 (br. s, 1H), 6.45 (d, *J* = 8.7 Hz, 1H), 7.09 (m, 2H); ¹³C-NMR (CDCl₃) δ 15.10, 22.25, 26.11 (q), 43.72 (s), 65.47 (d), 110.32 (s), 110.70, 125.47, 129.75 (d), 141.48, 148.33 (s); MS (EI) *m/z* 240, 242 (M+H)⁺.

A solution of 5-bromo-2,3,3-trimethyl-2,3-dihydro-1H-indole (0.5 g, 2.1 mmol) and tetrakis-(triphenylphosphine) palladium (0.14 g, 0.12 mmol) in
30 dimethoxyethane (10 mL) was cycled under N₂-vacuum (4x) and then stirred under

N₂ for 0.5 hours. To this mixture was then added 3-nitrophenylboronic acid (0.42 g, 2.5 mmol) followed by a solution of Na₂CO₃ (0.36 g, 3.4 mmol) in 5 mL water cycled under N₂-vacuum (3x). The solution was brought to reflux for 6 hours then cooled to room temperature, poured into water and extracted with EtOAc. The combined
5 organic extracts were washed with water, brine, dried (Na₂SO₄), and evaporated. The residue was purified by column chromatography (SiO₂, methylenechloride:hexane 1:3) to afford the title compound (0.48 g, 82%) as an orange semi-solid: ¹H NMR (CDCl₃) δ 1.12 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.35 (s, 3H), 3.60 (q, *J* = 6.6 Hz, 1H), 3.9 (br s, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 7.28-7.29 (m, 2H), 7.32 (d, *J* = 1.9 Hz,
10 1H), 7.53 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.0, 2.0 Hz, 1H), 8.07 (ddd, *J* = 7.9, 2.0, 2.0 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 8.39 (dd, *J* = 2.0, 2.0 Hz, 1H); ¹³C-NMR (CDCl₃) δ 15.27, 22.54, 26.39 (q), 43.53 (s), 65.57 (d), 109.48, 120.67, 121.04, 121.10, 126.58 (d), 129.15 (s), 129.53, 132.35 (d), 140.18, 143.64, 148.78, 150.11 (s); MS (EI) *m/z* 283 (M+H)⁺.

15

EXAMPLE 2

2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole Hydrochloride

A solution of 2,3,3-trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole (0.8 g, 2.79 mmol) in 20 mL of 1:1 ether:dioxane at room temperature was treated with 1.5
20 mL of a 4 M HCl/dioxane solution. The resulting solid was isolated by filtration and washed with hexane to afford the title compound (0.81 g, 90%) as a tan solid: m.p. 240-241 °; ¹H-NMR (CDCl₃) δ 1.37 (s, 3H), 1.51 (s, 3H), 4.01 (d, *J* = 6.5 Hz, 1H), 7.51 (s, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.7 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.8 (d, *J* = 7.9, Hz, 1H), 7.89 (d, *J* = 7.7 Hz, 1H), 8.3 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.42 (s, 1H), 11.9 (br
25 s, 2H); ¹³C-NMR (CDCl₃) δ; MS (EI) *m/z* 283 (M+H)⁺.

EXAMPLE 3

(2-R or S)-2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole and

and

EXAMPLE 4

30

(2-S or R)-2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole

A sample of racemic 2,3,3-trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole (25 mg), as prepared in example 2, was separated by a chiral preparative HPLC [column: Chiralcel OD, 4.6 X 250 mm, isocratic, 5:95 IPA:hexane, flow rate = 1 mL/min; injection volume = 5 μ L; retention times: 3, 9.2 min and 4, 10.39 min.] to provide the enantiomers 3 and 4 as orange semi-solids. Chiral Analytical HPLC determined that the enantiomers had > 99 % EE. Examples 3 and 4 have spectral data identical to the racemic material, example 1: ^1H -NMR (CDCl_3) δ 1.12 (s, 3H), 1.21 (d, $J = 6.6$ Hz, 3H), 1.35 (s, 3H), 3.60 (q, $J = 6.6$ Hz, 1H), 3.9 (br s, 1H), 6.69 (d, $J = 7.9$ Hz, 1H), 7.28-7.29 (m, 2H), 7.32 (d, $J = 1.9$ Hz, 1H), 7.53 (dd, $J = 7.9, 7.9$ Hz, 1H), 7.85 (ddd, $J = 7.9, 2.0, 2.0$ Hz, 1H), 8.07 (ddd, $J = 7.9, 2.0, 2.0$ Hz, 1H), 8.08 (d, $J = 7.9$ Hz, 1H), 8.39 (dd, $J = 2.0, 2.0$ Hz, 1H); MS (EI) m/z 283 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 5

2,3,3-Diethyl-2-methyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole
5-Bromo-3,3-diethyl-2-methyl-2,3-dihydro-1H-indole

This compound was prepared according to the procedure for Example 1 using 4-bromo-phenyl hydrazine hydrochloride (5.9 g, 26.3 mmol) and 3-ethyl-2-pentanone (3.0 g, 26.3 mmol). The subtitled compound (4.5 g) was obtained in 65 % yield as a yellowish oil: ^1H -NMR (CDCl_3) δ 0.81 (t, $J = 7.4$ Hz, 3H), 0.83 (t, $J = 7.4$ Hz, 3H), 1.18 (d, $J = 6.5$ Hz, 3H), 1.42 (dq, $J = 14.0, 7.4$ Hz, 1H), 1.66 (dq, $J = 14.0, 7.4$ Hz, 3H), 3.73 (q, $J = 6.5$ Hz, 1H), 6.47 (d, $J = 8.2$ Hz, 1H), 7.02 (d, $J = 2$ Hz, 1H), 7.09 (dd, $J = 8.2, 2.0$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 10.46, 10.66, 17.70 (q), 26.5, 29.67 (t), 52.25 (s), 64.80 (d), 111.64 (s), 112.41, 129.07, 131.58 (d), 139.57, 151.04 (s); MS (EI) m/z 268, 270 ($\text{M}+\text{H}$) $^+$.

Using the standard coupling conditions given in Example 1 the title compound was prepared from 5-bromo-3,3-diethyl-2-methyl-2,3-dihydro-1H-indole (0.13 g, 0.45 mmol), tetrakis-(triphenylphosphine) palladium (0.05 g, 0.04 mmol) in dimethoxyethane (4 mL) with 3-nitrophenylboronic acid (0.09 g, 0.54 mmol) and sodium carbonate (0.15 g, 4.95 mmol) in 2 mL of water. The title compound (0.09 g,

65%) was obtained as a red brown glass: ^1H NMR (CDCl_3) δ 0.86 (dt, $J = 4.0, 4.0$ Hz, 3H), 0.88 (dt, $J = 4.0, 4.0$ Hz, 3H), 1.24 (d, $J = 6.6$ Hz, 3H), 1.5 (dq, $J = 14.1, 7.3$ Hz, 1H), 1.66-1.84 (m, 3H), 3.81 (q, $J = 6.6$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 7.20 (d, $J = 1.9$ Hz, 1H), 7.32 (dd, $J = 8.0, 1.9$ Hz, 1H), 7.53 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.85 (dd, $J = 7.9, 1.1$ Hz, 1H), 8.09 (dd, $J = 7.9, 1.1$ Hz, 1H), 8.4 (dd, $J = 1.9$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 8.99, 9.14, 16.24 (q), 24.87, 28.14 (t), 50.30 (s), 63.31 (d), 109.56, 120.80, 121.22, 123.19, 126.76 (d), 128.64 (s), 129.67, 132.55 (d), 136.5, 143.92, 148.95, 151.07 (s); MS (EI) m/z 310 (M) $^+$.

10

EXAMPLE 6

4a-Methyl-6-(3-nitro-phenyl)-2,3,4,4a,9,9a-hexahydro-1H-carbazole
6-Bromo-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole

This compound was prepared by the procedure of Example 1 using 4-bromophenyl hydrazine hydrochloride (2.0 g, 8.95 mmol) and 2-methylcyclohexanone (1.0 g, 8.95 mmol). The subtitled compound (1.5 g, 65%) was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 1.26 (s, 3H), 1.38-1.46 (m, 4H), 1.56-1.68 (m, 4H), 3.4 (t, $J = 4.4$ Hz, 1H), 3.6 (br s, 1H), 6.53 (d, $J = 8$ Hz, 1H), 7.08 (d, $J = 2.0$ Hz, 1H), 7.09 (dd, $J = 8.0, 2.0$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 21.45, 21.87 (t), 23.96 (q), 27.92, 35.32 (t), 43.56 (s), 66.65 (d), 110.73 (s), 111.88, 125.25, 129.99 (d), 142.17, 149.03 (s); MS (EI) m/z 268, 270 (M+H) $^+$.

Using the standard coupling conditions given in Example 1, the title compound was prepared using 6-bromo-4a-methyl-2,3,4,4a,9,9a-hexahydro-1H-carbazole (1.6 g, 6.0 mmol), tetrakis(triphenylphosphine) palladium (0.4 g, 0.35 mmol) in dimethoxyethane (30 mL) with 3-nitrophenylboronic acid (1.2 g, 7.2 mmol) and sodium carbonate (1.9 g, 18 mmol) in 10 mL water. The pure product (1.2 g, 70%) was obtained as an orange foam: ^1H NMR (CDCl_3) δ 1.36 (s, 3H), 1.44-1.74 (m, 8H), 3.49 (t, $J = 4.4$ Hz, 1H), 3.83 (br s, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 1.9$ Hz, 1H), 7.32 (dd, $J = 8.0, 1.9$ Hz, 1H), 7.53 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 8.08 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.39 (dd, $J = 2.0, 2.0$ Hz, 1H); ^{13}C -NMR (CDCl_3) δ 21.27, 21.71 (t), 23.87 (q), 27.76, 35.29 (t), 43.06 (s), 66.46 (d), 110.41,

120.57, 120.83, 121.24, 126.55 (d), 129.26 (s), 129.68, 132.55 (d), 140.66, 143.86, 148.95, 150.51 (s); MS (EI) m/z 309 (M+H)⁺.

EXAMPLE 7

5 1,2-Dihydro-2-methyl-5-(3-nitro-phenyl)spiro[cyclohexane-1,3-[3H]indole]
 5-Bromo-1,2-dihydro-2-methylspiro[cyclohexane-1,3-[3H] indole]

Using the conditions given in Example 1 the subtitled compound was prepared from 4-bromo-phenyl hydrazine HCl (3.5 g, 15.7 mmol) and cyclohexyl methyl ketone (2.0 g, 15.7 mmol). The pure material (3.0 g, 68%) was obtained as an oil: ¹H
10 NMR (CDCl₃) δ 1.09 (d, J = 6.5 Hz, 3H), 1.25-1.73 (m, 10H), 3.45 (br s, 1H), 3.71 (q, J = 6.5 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 7.09 (dd, J = 8.2, 2.0 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H); ¹³C-NMR (CDCl₃) δ 17.22 (q), 23.19, 23.44, 26.16, 30.17, 36.70 (t), 47.99 (s), 62.34 (d), 110.08 (s), 111.07, 126.83, 130.08 (d), 139.98, 148.49 (s); MS (EI) m/z 280, 282 (M+H)⁺.

15 Using the standard coupling conditions given in Example 1 the title compound was prepared from 5-bromo-1,2-dihydro-2-methylspiro[cyclohexane-1,3-[3H] indole] (0.5 g, 1.65 mmol), tetrakis(triphenylphosphine) palladium (0.08 g, 0.07 mmol) in dimethoxy-ethane (5 mL) with 3-nitrophenylboronic acid (0.33 g, 1.98 mmol) and sodium carbonate (0.53 g, 4.95 mmol) in 5 mL water. The pure material (0.35 g,
20 55%) was obtained as an orange brown semi-solid: ¹H NMR (CDCl₃) δ 1.16 (d, J = 6.4 Hz, 3H), 1.38-1.83 (m, 10H), 3.7 (br s, 1H), 3.8 (q, J = 6.4 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.0, 1.8 Hz, 1H), 7.53 (dd, J = 8.0, 8.0 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.39 (dd, J = 1.9, 1.9 Hz, 1H); ¹³C-NMR (CDCl₃) δ 17.45 (q), 23.32, 23.70, 26.21, 30.31, 37.07 (t), 47.77 (s), 62.11 (d),
25 109.81, 120.78, 121.23, 122.40, 126.92 (d), 128.96 (s), 129.66, 132.51 (d), 138.63, 143.92, 148.94, 150.1 (s); MS (EI) m/z 322 (M)⁺.

EXAMPLE 8

30 3,3-Dimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole (WAY-160655)
 3,3-dimethyl-1,3-dihydro-2H-indol-2-one

This compound was prepared using the general method described by A. Kende, *Synth. Commun.*, **1**: 12 (1982). The crude material was purified by column chromatography (SiO₂, methylenechloride:hexane 1:3) to afford the subtitled compound which was consistent with the reported spectral data.

5 The above oxindole (0.65 g, 4.03 mmol) and sodium acetate (0.334 g, 4.07 mmol) were stirred in acetic acid (5.0 mL). Bromine (0.66 g, 0.00413 mol) in acetic acid (5.0 mL) was added drop-wise to the reaction mixture. The reaction was stirred for 50 minutes, and then poured into water (10 mL). The mixture was made basic with sodium carbonate, extracted with ethyl acetate, dried (MgSO₄), filtered, and
10 evaporated to give 5-bromo-1,3-dihydro-3,3-dimethyl-2H-indol-2-one (0.89 g, 92%):
 ¹H NMR (DMSO-d₆) 1.21 (s, 6 H), 6.76 (d, *J* = 8.22 Hz, 1H), 7.29 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 10.4 (s, 1H).

 To a solution of the 5-bromo-1,3-dihydro-3,3-dimethyl-2H-indol-2-one (0.9 g, 3.7 mmol) in 20 mL THF at 0 °C was added a borane-methylsulfide complex (2M in
15 THF, 38 mL, 75 mmol). The reaction mixture was warmed to room temperature then brought to reflux for 4 hours. The mixture was cooled to room temperature and poured into H₂O/CH₂Cl₂ and washed with 5% NaHCO₃. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. The crude product was extracted in MeOH, trimethylamine N-oxide (2.0 g, 26.6 mmol) was added, and the
20 solution was brought to reflux for 2 hours. The reaction mixture was cooled, concentrated and the crude residue purified by column chromatography (SiO₂, methylene chloride) to afford 5-bromo-3,3-dimethyl-2,3-dihydro-1H-indole (0.074 g, 87%) as a yellow oil: ¹H NMR (CDCl₃) δ 1.29 (s, 6H), 3.30 (s, 2H), 3.5 (br s, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 7.08-7.12 (m, 2H); ¹³C-NMR (CDCl₃) δ 27.69 (q), 42.21 (s),
25 62.01 (d), 110.38 (s), 111.09, 125.46, 130.09 (d), 141.03, 149.52 (s); MS (EI) *m/z* 225, 227 (M)⁺.

 Using the standard coupling conditions given in Example 1, the title compound was prepared from 5-bromo-3,3-dimethyl-2,3-dihydro-1H-indole (0.25 g, 1.1 mmol), tetrakis(triphenylphosphine) palladium (0.08 g, 0.07 mmol) in
30 dimethoxyethane (5 mL) with 3-nitrophenylboronic acid (0.22 g, 1.3 mmol) and

sodium carbonate (0.35 g, 3.3 mmol) in 5 mL water. The title compound (0.17 g, 60%) was obtained as a brown semi-solid: ^1H NMR (CDCl_3) δ 1.38 (s, 3H), 3.40 (s, 2H), 6.72 (d, $J = 8.0$ Hz, 1H), 7.29-7.34 (m, 2H), 7.54 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 8.09 (dd, $J = 8.0, 1.5$ Hz, 1H), 8.40 (dd, $J = 2.0, 2.0$ Hz, 1H); ^{13}C -
5 NMR (CDCl_3) δ 27.89 (q), 41.93 (s), 62.05 (d), 109.78, 120.87, 121.02, 121.23, 126.87 (d), 129.19 (s), 129.69, 132.52 (d), 139.64, 143.75, 148.94, 151.17 (s); MS (EI) m/z 268 (M) $^+$.

EXAMPLE 9

10 5'-(3-Chlorophenyl)-1',2'-dihydrospiro[cyclohexane-1,3'-[3H]indole]
Spiro [cyclohexane-1,3'-[3H]indol]-2'-(1'H) one

A solution of the oxindole (25g, 190 mmol) in 800 mL of anhydrous THF was cooled to -20°C , *n*-butyllithium (2.5M in hexanes, 152 mL, 0.38 mol) slowly added, followed by the addition of N,N,N',N'-tetramethylenediamine (51 mL, 0.38 mol).
15 After 15 minutes, 1,5-diiodopentane (174g, 0.54 mol) was added slowly and the mixture was allowed to warm to room temperature. After stirring for 16 hours saturated aqueous ammonium chloride solution (1L) and ethylacetate (1L) were added. After 15 minutes, the layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were extracted with
20 hydrochloric acid (1N, 500 mL), then washed with brine, dried (MgSO_4), and concentrated to obtain an oil. The oil was triturated with hexane (200 mL) and benzene (20 mL). The precipitate was collected and dried *in vacuo* to provide Spiro [cyclohexane-1,3'-[3H]indol]-2'-(1'H) one (26.3g, 69.6%) as colorless crystals: mp $110-114^\circ$; ^1H NMR ($\text{DMSO}-d_6$) δ 1.67 (m, 10H), 6.84 (d, 1H, $J = 8$ Hz), 6.94 (t, 1H, $J = 8$ Hz), 7.17 (t, 1H, $J = 8$ Hz), 7.44 (d, 1H, $J = 8$ Hz), 10.3 (s, 1H).
25

To a solution of the above oxindole (17.6 g, 90.0 mmol) in acetic acid (300 mL) was added sodium acetate (8.0 g, 100.0 mmol) and bromine (14.6g, 91.0 mmol) with stirring. After 30 minutes at room temperature, the reaction mixture was partitioned between water and ethylacetate. The aqueous phase was extracted with
30 ethylacetate. The combined organic layers were washed with water, dried (MgSO_4)

and evaporated. The residue was triturated with hexane. The precipitate was collected, and dried *in vacuo* to provide 5-Bromo-spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one (16.5g, 67%) as off-white crystals: m.p. 196-199°; ¹H NMR (DMSO-d₆) δ 1.62 (m, 10H), 6.8 (d, 1H, *J* = 6.8 Hz), 7.36 (d, 1H, *J* = 8.2, 1.8 Hz), 7.58 (dd, 1H, *J* = 8.2, 1.8 Hz), 10.44 (s, 1H).

Using the standard coupling conditions given in Example 1, the title compound was prepared from the above bromo-oxindole (0.32 g, 1.14 mmol) tetrakis(triphenylphosphine) palladium (0.08g, 0.07 mmol) and 3-chlorophenylboronic acid (0.21 g, 1.37 mmol), and sodium carbonate (0.36 g, 3.4 mmol) in water (3 mL). 5-(3-chlorophenyl)-spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one (0.28 g, 80%) was obtained as a yellow solid: m.p. 164-165 °; ¹H NMR (CDCl₃) δ 1.60-1.78 (m, 6H), 1.81-1.99 (m, 4H), 7.04 (d, *J* = 8.1 Hz, 1H), 7.22-7.47 (m, 4H), 7.53 (s, 1H), 7.61 (s, 1H), 9.28 (br s, 1H); ¹³C-NMR (CDCl₃) δ 20.17, 24.12, 31.92 (t), 47.22 (s), 109.21, 121.94, 124.06, 125.50, 125.79, 125.97, 126.38, 128.96 (d), 132.88, 133.59, 135.60, 139.14, 142.17, 182.89 (s); MS (EI) *m/z* 310, 312 (M-H)⁺.

To a solution of 5-(3-chlorophenyl)-spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one (0.42 g, 1.4 mmol) in 20 mL THF at 0 °C is added borane-dimethylsulfide complex, (2M in THF, 14 mL, 28 mmol). The reaction mixture was warmed to room temperature then brought to reflux for 4 hours. The mixture was cooled to room temperature and poured into H₂O with CH₂Cl₂ and washed with 5% NaHCO₃. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The crude product was extracted in MeOH and trimethylamine N-oxide (1.0 g, 9.0 mmol) was added. The solution was brought to reflux for 2 hours, the mixture was cooled, concentrated and the crude residue purified by column chromatography (SiO₂, methylene chloride) to afford the title compound (0.25 g, 63%) as a yellow oil: ¹H NMR (CDCl₃) δ 1.3-1.55 (m, 3H), 1.6-1.85 (m, 7H), 3.1 (br s, 1H), 3.5 (s, 2H), 6.6 (d, *J* = 8.0 Hz, 1H), 7.18-7.32 (m, 4H), 7.4 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.5 (s, 1H); ¹³C-NMR (CDCl₃) δ 23.65, 26.24, 37.00 (t), 46.58 (s), 57.49 (t), 109.95, 121.82, 125.07, 126.36, 126.98, 127.08, 130.29 (d), 130.64, 134.91, 139.65, 144.29, 151.09 (s); MS (EI) *m/z* 298, 300 (M+H)⁺.

EXAMPLE 10

3-(2',3',3'-trimethyl-2',3-dihydro-1H-indol-5'-yl) benzonitrile

To a solution of 5-bromo-2,3,3-trimethyl-2,3-dihydro-1H-indole (2.03 g, 8.45 mmol) in dimethoxyethane (50 mL), under nitrogen was added tetrakis(triphenylphosphine)palladium (0.47 g, 0.4 mmol). After 20 minutes at room temperature, 3-formylphenylboronic acid (2.36 g, 16.4 mmol) and potassium carbonate (6.80 g, 55 mmol) in water (25 mL) was added, and the mixture was heated under reflux. After 2 hours, the mixture was cooled, poured into brine and extracted with EtOAc (x 2). The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. The residue was then subjected to column chromatography (SiO₂, EtOAc: hexane, 1:8) to afford 3-(2,3,3'-trimethyl-2',3-dihydro-1H-indol-5'-yl) benzaldehyde (0.96 g, 3.62 mmol, 43 %) as a slightly impure solid that was used without further purification: ¹H NMR (CDCl₃) δ 1.11 (s, 3H), 1.22 (d, 3H, *J* = 6.5 Hz), 1.35 (s, 3H), 3.59 (dd, 1H, *J* = 13, 7 Hz), 6.69 (d, 1H, *J* = 1 Hz), 7.25 (s, 1H), 7.32 (s, 1H), 7.55 (t, 1H, *J* = 7.6 Hz), 7.80 (d, 1H, *J* = 1 Hz), 7.82 (d, 1H, *J* = 1 Hz), 8.05 (s, 1H), 10.07 (s, 1H).

To a solution of the above compound (0.96 g, 3.62 mmol) in MeCN/H₂O (20 mL, 95:5) was added hydroxylamine hydrochloride (0.82 g, 7.25 mmol). After 1 hour, the mixture was poured into a saturated sodium hydrogen carbonate solution and extracted with EtOAc (x2). The combined organic extracts were washed with water, dried (MgSO₄) and evaporated. The residue was then dissolved in dichloromethane (20 mL) and treated with thionyl chloride (0.53 mL, 7.25 mmol). After 16 hours, the mixture was quenched with saturated sodium hydrogen carbonate solution and concentrated, partitioned between water and EtOAc, and re-extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO₄) and evaporated. Purification by column chromatography (EtOAc: hexane, 1:8) afforded a yellow oil (0.31 g) which was dissolved in methanol (5 mL) and treated with ethereal hydrogen chloride (1M, 1.3 mL, 1.3 mmol) and evaporated. Recrystallization from MeOH/Et₂O then afforded the title compound (0.20 g, 0.60

mmol, 18 %): mp >235 °C (decomp); ¹H NMR (CDCl₃) δ 1.57 (s, 3H), 1.36 (d, 3H, *J* = 6.7 Hz), 1.40 (s, 3H), 3.72-3.76 (m, 1H), 7.30 (d, 1H, *J* = 8 Hz), 7.67 (t, 2H, *J* = 7 Hz), 7.79 - 7.84 (m, 2H), 8.03 (d, 1H, *J* = 8 Hz), (8.2, s, 1H); MS (EI) *m/z* 262 (M)⁺.

5

EXAMPLE 11 - Pharmacology

The biological activity for the compounds of the current invention was evaluated in the in-vitro assays described below. In-vitro potencies lie in the range 0.01 nM - 10,000 nM, and in-vivo potencies in the range 1 µg/kg to 100 mg/kg.

The in-vitro biology is determined by (1) competitive radioligand Binding:
10 using the A-form of the human progesterone receptor with progesterone as the radioligand; (2) co-transfection assay, which provides functional activity expressed as agonist EC₅₀ and Antagonist IC₅₀ values; and (3) a T47D cell proliferation, which is a further functional assay which also provides agonist and antagonist data.

1. hPR Binding assay - This assay is carried out in
15 accordance with: Pathirana, C.; Stein, R.B.; Berger, T.S.; Fenical, W.; Ianiro, T.; Mais, D.E.; Torres, A.; Glodman, M.E., Nonsteroidal human progesterone receptor modulators from the marine alga cymoplia barbata, J. Steroid Biochem. Mol. Biol., 1992, 41, 733-738.

2. PRE-luciferase assay in CV-1 cells

20 The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Medium: The growth medium was as follows:
25 DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). The experimental medium was as follows: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino

acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Cell culture, transfection, treatment, and luciferase assay

- 5 Stock CV-1 cells are maintained in growth medium. Co-transfection is done using 1.2×10^7 cells, 5 mg pLEM plasmid with hPR-B inserted at SphI and BamHI sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II.
- 10 After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 μ l. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test compounds in experimental medium. Compounds are tested for antiprogesterational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the
- 15 medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty μ l of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

- 20 Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way
- 25 analysis of variance and non-linear response analyses.

d. Reference Compounds:

- Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogesterin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 1. Estimated EC₅₀, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

5	Compound	Exp.	EC ₅₀	SE	95% CI	
			(nM)		lower	upper
	Progesterone	1	0.616	0.026	0.509	0.746
		2	0.402	0.019	0.323	0.501
		3	0.486	0.028	0.371	0.637
10	Trimegestone	1	0.0075	0.0002	0.0066	0.0085
		2	0.0081	0.0003	0.0070	0.0094
		3	0.0067	0.0003	0.0055	0.0082

Table 2. Estimated IC₅₀, standard error (SE), and 95% confident interval (CI) for the antiprogesterin, RU486 from three individual studies

15	Compound	Exp.	IC ₅₀	SE	95% CI	
			(nM)		lower	upper
20	RU486	1	0.028	0.002	0.019	0.042
		2	0.037	0.002	0.029	0.048
		3	0.019	0.001	0.013	0.027

Progestational activity: Compounds that increase PRE-luciferase activity significantly ($p < 0.05$) compared to vehicle control are considered active.

25 Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly ($p < 0.05$)

EC₅₀: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

30 IC₅₀: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

3. T47D cell proliferation assay

The objective of this assay is the determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured. The materials and methods used in this assay are as follows.

a. Growth medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Treatment medium: Minimum Essential Medium (MEM) (#51200-038 GIBCO, BRL) phenol red-free supplemented with 0.5% charcoal stripped fetal bovine serum, 100U/ml penicillin, 200 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

c. Cell culture

Stock T47 D cells are maintained in growth medium. For BrdU incorporation assay, cells are plated in 96-well plates (Falcon, Becton Dickinson Labware) at 10,000 cells/well in growth medium. After overnight incubation, the medium is changed to treatment medium and cells are cultured for an additional 24 hr before treatment. Stock compounds are dissolved in appropriate vehicle (100% ethanol or 50% ethanol/50% DMSO), subsequently diluted in treatment medium and added to the cells. Progesterone and antiprogestin reference compounds are run in full dose-response curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogestins are tested in the presence of 0.03 nM trimegestone, the reference progesterone agonist. Twenty-four hours after treatment, the medium is discarded and cells are labeled with 10 mM BrdU (Amersham Life Science, Arlington Heights, IL) in treatment medium for 4 hr.

d. Cell Proliferation Assay

At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an ethanol containing fixative for 30 min, followed by incubation in a blocking buffer

for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and incubated with 3,3',5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min depending upon the potency of tested compounds. Then 25 μ l of 1 M sulfuric acid is added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

e. Analysis of Results:

Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. EC_{50} or IC_{50} values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

Trimegestone and medroxyprogesterone acetate (MPA) are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 3. Estimated EC_{50} , standard error (SE), and 95% confidence intervals (CI) for individual studies

Compound	Exp	EC_{50} (nM)	SE	<u>95% CI</u>	
				lower	upper
Trimegestone	1	0.017	0.003	0.007	0.040
	2	0.014	0.001	0.011	0.017
	3	0.019	0.001	0.016	0.024
MPA	1	0.019	0.001	0.013	0.027
	2	0.017	0.001	0.011	0.024

Table 4. Estimated IC_{50} , standard error, and 95% confident interval for the antiprogesterin, RU486

5	Compound	Exp	IC_{50} (nM)	SE	<u>95% CI</u>	
					lower	upper
	RU486	1	0.011	0.001	0.008	0.014
		2	0.016	0.001	0.014	0.020
		3	0.018	0.001	0.014	0.022

- 10 EC_{50} : Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; IC_{50} : Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE.

All above-noted published references are incorporated herein by reference.

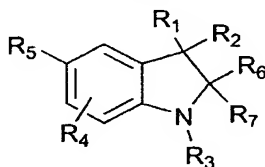
- 15 Numerous modification and variations of the present invention are included in the above-identified specification are expected to be obvious to one of skill in the art. Such modifications and alterations to the methods, solutions, apparatuses of the present invention are believed to be encompassed in the scope of the claims appended hereto.

What is Claimed:

1. A method of contraception which comprises administering to a female of child bearing age for 28 consecutive days:

a) a first phase of from 14 to 24 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 μ g levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units, at a daily dosage of from about 2 to 50 mg, of an antiprogesterin compound of Formula I:



I

wherein:

R_1 and R_2 are chosen independently from H, alkyl, substituted alkyl; OH; O(alkyl); O(substituted alkyl); OAc; aryl; optionally substituted aryl; heteroaryl; optionally substituted heteroaryl; alkylaryl; alkylheteroaryl; 1-propynyl; or 3-propynyl;

or R_1 and R_2 are joined to form a ring comprising $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$; $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$; $-\text{O}(\text{CH}_2)_m\text{CH}_2-$; $\text{O}(\text{CH}_2)_p\text{O}-$; $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$; $-\text{CH}_2\text{CH}_2\text{N}(\text{alkyl})\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2-$;

n is an integer from 0 to 5;

m is an integer from 1 to 4;

p is an integer from 1 to 4;

or R_1 and R_2 together comprise a double bond to $=\text{C}(\text{CH}_3)_2$; $=\text{C}(\text{C}_3-\text{C}_6 \text{ cycloalkyl})$, $=\text{O}$, or $=\text{C}(\text{cycloether})$, wherein cycloether is selected from tetrahydrofuranyl or hexahydropyranyl;

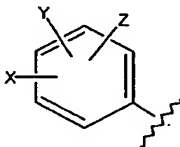
R_3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, alkynyl or substituted alkynyl, or COR^A ;

R^A = H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R_4 = H, halogen, CN, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R_5 is selected from the groups a), b) or c):

a) R_5 is a benzene ring of the formula:



X is selected from halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, $S(O)alkyl$, $S(O)_2alkyl$, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^B , $OCOR^B$, or $NR^C COR^B$;

R^B is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl:

Y and Z are independently selected from H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkyl;

or

b) R₅ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR₆ and containing one or two independent substituents from the group including H, halogen, CN, NO₂ and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^D, or NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

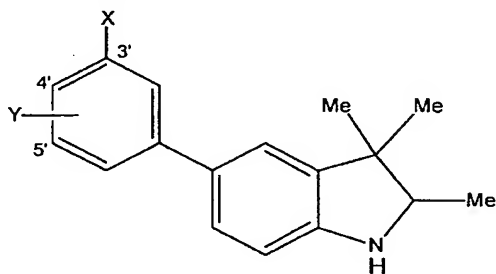
R₆ is H or C₁ to C₃ alkyl;

or

c) R⁵ is an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, the moiety being optionally substituted by from 1 to 3 substituents selected from halogen, lower alkyl, CN, NO₂, lower alkoxy, or CF₃; wherein R₆ and R₇ are independently chosen from H, methyl, ethyl, propyl, butyl, iso-propyl, iso-butyl, cyclohexyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl; or pharmaceutically acceptable salt thereof; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo for the remaining days of the 28 consecutive days in which no antiprogesterin, progesterin or estrogen is administered; wherein the total daily dosage units of the first, second and third phases equals 28.

2. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



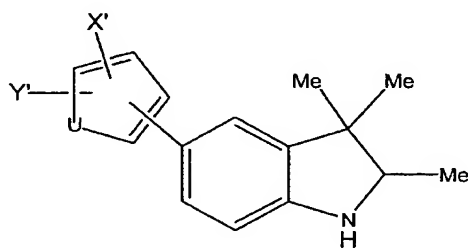
wherein:

X is selected from halogen, CN, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5-membered heterocyclic ring containing 1 to 3 heteroatoms, or C₁ to C₃ thioalkoxy;

Y is a substituent on the 4' or 5' position selected from H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, or C₁ to C₃ thioalkyl;

or pharmaceutically acceptable salt thereof.

3. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

U is O, S, or NR_6 ,

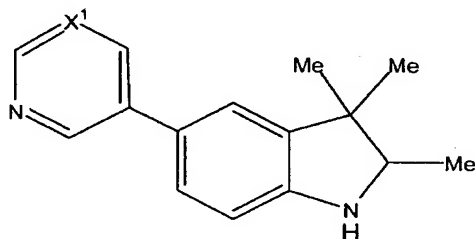
R_6 is H, or C_1 to C_3 alkyl, or C_1 to C_4 CO_2 alkyl;

X' is selected from halogen, CN, NO_2 , C_1 to C_3 alkyl or C_1 to C_3 alkoxy;

Y' is selected from the group H, F, CN, NO_2 or C_1 to C_4 alkyl;

or pharmaceutically acceptable salt thereof.

4. A method of Claim 1 wherein the progestational agent is levonorgestrel and the anti-progestin compound has the structure:



wherein:

X^1 is N or CX^2 ;

X^2 is halogen, CN or NO_2 ;

or pharmaceutically acceptable salt thereof.

5. A method of Claim 1 wherein the antiprogestin compound is 2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole or a pharmaceutically acceptable salt thereof.

6. A method of Claim 1 wherein the antiprogestin compound is 2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole Hydrochloride or a pharmaceutically acceptable salt thereof.

7. A method of Claim 1 wherein the antiprogestin compound is (2-R)-2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole or a pharmaceutically acceptable salt thereof.

8. A method of Claim 1 wherein the antiprogestin compound is (2-S)-2,3,3-Trimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole or a pharmaceutically acceptable salt thereof.

9. A method of Claim 1 wherein the antiprogestin compound is 2,3,3-Diethyl-2-methyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole or a pharmaceutically acceptable salt thereof.

10. A method of Claim 1 wherein the antiprogestin compound is 4a-Methyl-6-(3-nitro-phenyl)-2,3,4,4a,9,9a-hexahydro-1H-carbazole or a pharmaceutically acceptable salt thereof.

11. A method of Claim 1 wherein the antiprogestin compound is 1,2-Dihydro-2-methyl-5-(3-nitro-phenyl)spiro[cyclohexane-1,3-[3H]indole] or a pharmaceutically acceptable salt thereof.

12. A method of Claim 1 wherein the antiprogestin compound is 3,3-Dimethyl-5-(3-nitro-phenyl)-2,3-dihydro-1H-indole or a pharmaceutically acceptable salt thereof.

13. A method of Claim 1 wherein the antiprogestin compound is 5'-(3-Chlorophenyl)-1',2'-dihydrospiro[cyclohexane-1,3'-[3H]indole] or a pharmaceutically acceptable salt thereof.

14. A method of Claim 1 wherein the antiprogestin compound is 3-(2',3',3'-trimethyl-2',3-dihydro-1H-indol-5'-yl) benzonitrile or a pharmaceutically acceptable salt thereof.

15. The method of Claim 1 wherein the progestational agent is selected from the group of levonorgestrel, norgestrel, desogestrel, 3-ketodesogestrel, norethindrone, gestodene, norethindrone acetate, norgestimate, osaterone, cyproterone acetate, trimegestone, dienogest, drospirenone, norgestrol, or (17-deacetyl)norgestimate.

16. A method of Claim 1 which comprises administering to a female of child bearing age consecutively over a 28 day cycle:

- a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 100 µg levonorgestrel;
- b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and
- c) optionally, 4 daily dosage units of an orally and pharmaceutically acceptable placebo to be administered on each day of the 28-day cycle following the first phase and second phase.

17. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

- a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 µg levonorgestrel, and ethinyl estradiol at a daily dose range of from about 10 to about 35 µg; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, an orally and pharmaceutically acceptable placebo for each remaining day of the 28 consecutive days.

18. A method of contraception of Claim 17 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 100 μ g levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μ g; and

b) a second phase of 3 daily dosage units of an antiprogestin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

19. A method of contraception which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of from 18 to 21 daily dosage units containing a progestational agent at a daily dose equal in progestational activity to from about 35 to about 150 μ g levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μ g

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg and ethinyl estradiol at a concentration of from about 10 to about 35 μ g; and

c) optionally, a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo, the total of the daily dosage units being 28.

20. A method of contraception of Claim 19 which comprises administering to a female of child bearing age over a period of 28 consecutive days:

a) a first phase of 21 daily dosage units, each daily dosage unit containing a progestational agent at a daily dose equal in progestational activity to about 35 to about 100 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of 3 daily dose, each daily dose unit containing an antiprogestin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg ; and

c) optionally, a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

21. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 14 to 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel;

b) a second phase of from 1 to 11 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

22. A pharmaceutically useful kit adapted for daily oral administration of Claim 21 which comprises:

a) a first phase of 21 daily dosage units of a progestational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel;

b) a second phase of 3 daily dosage units of an antiprogestin compound of Claim 1, each daily dosage unit containing an antiprogestin compound at a daily dosage of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

23. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 18 to 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg ; and

b) a second phase of from 1 to 7 daily dosage units of an antiprogesterin of Claim 1 at a daily dose of from about 2 to 50 mg; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

24. A pharmaceutically useful kit adapted for daily oral administration of Claim 23 which comprises:

a) a first phase of 21 daily dosage units of a progestostational agent equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg ; and

b) a second phase of three daily dosage units of an antiprogesterin of Claim 1 administered at a daily dose of from about 2 to 50 mg; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

25. A pharmaceutically useful kit adapted for daily oral administration which comprises:

a) a first phase of from 18 to 21 daily dosage units, each daily dosage unit comprising a progestational agent at a daily dose equal in progestational activity to

from about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of from 1 to 7 daily dose units, each daily dose unit containing an antiprogesterin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg ; and

c) a third phase of from 0 to 9 daily dosage units of an orally and pharmaceutically acceptable placebo;

wherein the total number of the daily dosage units in the first phase, second phase and third phase equals 28.

26. A pharmaceutically useful kit adapted for daily oral administration of Claim 25 which comprises:

a) a first phase of 21 daily dosage units, each containing a progestational agent of this invention at a daily dose equal in progestational activity to about 35 to about 150 μg levonorgestrel and ethinyl estradiol at a daily dose range of from about 10 to about 35 μg

b) a second phase of 3 daily dose units, each daily dose unit containing an antiprogesterin of Claim 1 at a concentration of from 2 to 50 mg; and ethinyl estradiol at a concentration of from about 10 to about 35 μg ; and

c) a third phase of 4 daily dosage units of an orally and pharmaceutically acceptable placebo.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/11748

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K45/06 A61P15/18 //A61K31/57,31:40,31:565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 43 30 234 A (SCHERING AG) 9 March 1995 (1995-03-09) column 1, line 1 - line 30 claims 1-8	1-26
A	WO 96 15794 A (BALANCE PHARMACEUTICALS INC) 30 May 1996 (1996-05-30) page 6, line 15 -page 7, line 23	1-26
A	WO 97 49407 A (AKZO NOBEL NV ;COELINGH BENNINK HERMAN JAN TI (NL); VERBOST PIETER) 31 December 1997 (1997-12-31) page 2, line 29 -page 3, line 6	1-26
A	US 5 521 166 A (GRUBB GARY S) 28 May 1996 (1996-05-28) claim 1 column 2, line 41 - line 60	1-26
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

28 September 2000

Date of mailing of the international search report

11/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bonzano, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/11748

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 483 077 A (I F L O S A S DI GIORGIO E ALD) 29 April 1992 (1992-04-29) page 2, line 1 - line 10 claims 1,21 ---	1-26
A	WO 98 55116 A (GOULET MARK ;MERCK & CO INC (US); WALSH THOMAS F (US); UJJAINWALLA) 10 December 1998 (1998-12-10) claim 12 -----	1-26

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,15-26 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Present claims 1,5-14,16-26 relate to a compound defined by reference to a desirable characteristic or property, namely the activity as progestational.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the combinations of the progestationals and the antiprogestinics explicitly mentioned in the claims, with due regard to the general idea underlying the present invention.

Claims searched completely: 2-4.

Claims searched incompletely: 1-3,5-26.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter nal Application No

PCT/US 00/11748

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